REMARKS

Upon entry of this amendment, claims 1, 6, 7, 16-18, 26, 27, and 71-73 will be pending in the application. Claims 2-5, 8-15, 19-25, and 28-70 have been canceled. Claims 1, 6, 7, 16-18, 27, and 71 are amended herein to recite a dominant negative mismatch repair protein truncation mutant, as supported by the specification, for example, at page 11, lines 11-13 and the original claims. Claims 72 and 73 are amended to recite a dominant negative mismatch repair protein, as likewise supported by the specification, for example, at page 11, lines 9-13 and page 18, lines 4-16. The claims, which recite mismatch repair proteins that exert a dominant negative effect, encompass truncation mutants disclosed by the specification and as known in the art for MutS and MutL, as well as overexpression of eukaryotic mismatch repair proteins, which exerts a dominant negative effect on bacterial mismatch repair. No new matter is introduced by this amendment.

Applicants note with appreciation the withdrawal of the rejections under 35 U.S.C. § 102(b) of claim 18 over Aronshtam *et al.* (*Nuc. Acids Res.*, 24:2498-2504 (1996)) and claims 1 and 18 over Prudhomme *et al.* (*J. Bacteriol.*, 173:7196-7203 (1991)). Applicants further note with appreciation the withdrawal of the rejection of claims 12, 16, and 71 under 35 U.S.C. § 112, second paragraph.

Applicants respectfully request reconsideration of allowance of the claims.

Amended claims 6 and 7 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph.

Claims 6 and 7 are rejected under the second paragraph of 35 U.S.C. § 112 for alleged failure to particularly point out and distinctly claim the subject matter Applicants regard as their invention. Applicants have amended claims 6 and 7 to recite "mismatch repair protein," thereby providing clear antecedent basis in claim 1 as amended. Applicants respectfully request withdrawal of the rejection.

Amended claims 1, 6, 7, 12, 14-16, 18, 26, 27, and 71-73 comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

Claims 1, 6, 7, 12, 14-16, 18, 26, 27, and 71-73 remain rejected under the first paragraph of 35 U.S.C. § 112 as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Office Action, the specification does not contain adequate written description of a dominant negative effect of (1) any *PMS2* gene from any species other than human or *Arabidopsis* in (2) any bacterium. (Office Action at page 6.) Preliminarily, Applicants note that the cancellation of claims 12, 14, and 15 without prejudice renders the rejection of those claims moot. To the extent the rejection applies to the amended claims, Applicants traverse.

The statutory authority for the written description requirement is 35 U.S.C. § 112, first paragraph, which states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Compliance with the written description requirement of 35 U.S.C. § 112, first paragraph requires sufficient information in the original disclosure to convince an ordinarily skilled artisan that the inventor possessed the invention at the time of filing. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003). The United States Patent and Trademark Office has determined that possession can be demonstrated by a disclosure of functional characteristics when coupled with a known or disclosed correlation between function and structure. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001).

The pending independent claims are claims 1, 18, 72, and 73. Amended claims 1 and 72 encompass methods for making a hypermutable bacterium by introducing into a bacterium a polynucleotide encoding a dominant negative PMS2 mismatch repair protein truncation mutant or dominant negative PMSR or PMS2L mismatch repair protein under the control of

an inducible transcription regulatory sequence and inducing expression of the mismatch repair protein to exert a dominant negative effect on mismatch repair, thereby making the bacterium hypermutable. Amended claims 18 and 73 are directed to homogeneous compositions of induced, cultured, hypermutable bacteria having a polynucleotide encoding a dominant negative PMS2 mismatch repair protein truncation mutant (claim 18), or PMSR or PMS2L mismatch repair protein (claim 73) under the control of an inducible transcription regulatory sequence, wherein the dominant negative mismatch repair protein exerts a dominant negative effect when expressed.

Applicants respectfully submit that one of ordinary skill in the art having read the present specification would readily envisage the bacterial cell types, PMS2 proteins from a variety of species, and various dominant negative PMS2 proteins that fall within the scope of the pending claims.

In rejecting a claim under the written description requirement of 35 U.S.C. §112, first paragraph, the Patent Office has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). In making the rejection, the Patent Office is required: (1) to set forth the claim limitation not described; and (2) to provide reasons why a person skilled in the art would not have recognized the description of the limitation in view of the disclosure of the application as filed. Manual of Patent Examining Procedure, § 2163.04.

One of ordinary skill in the art would readily visualize and recognize the identity of the bacteria encompassed by the claims

The office action asserts that the specification fails to adequately describe the genus of bacterial species encompassed within the scope of the claims. (Office Action at page 6.) Applicants respectfully traverse.

The Federal Circuit has recently found that a generic disclosure of large classes of cells is adequate, without naming or exemplifying large numbers of such cells. In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) the Federal Circuit held that vertebrate cells and mammalian cells were adequately described. Because the cells are known biological materials rather than genetic materials, the court held that the holding of

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) was inapposite. *Amgen* at 1332. The court held that "vertebrate cells" and "mammalian cells" conveyed to the ordinarily skilled artisan adequate information to visualize or recognize the identity of the members of the genus. *Amgen* at 1332. The court further held the disclosed production of EPO polypeptide in just two species of the disclosed genus of cells adequately supported the claimed production of the EPO polypeptide in the full genus of cells. *Amgen* at 1332.

Similarly, the present claims are directed to methods and compositions involving bacterial cells. The bacterial cells of the invention are described in the specification as "any species for which suitable techniques are available to produce transgenic microorganisms, such as but not limited to genera including *Bacillus*, *Pseudomonas*, *Staphylococcus*, *Escherichia*, and others." (Specification, page 14, lines 10-13.) Because bacterial cell types suitable for use in the invention are known biological materials, the term "bacteria" conveys to the ordinarily skilled artisan adequate information to visualize and recognize the identity of members of the genus.

The office action also asserts that the specification is deficient in showing that PMS2 genes would cause hypermutability in any bacterium. (Office Action at pages 4-5.) The office action has supplied no reasoning to doubt that bacteria other than the specifically disclosed DH10B and BL21 strains (Examples 2 and 3) would become hypermutable upon expression of a dominant negative mismatch repair protein. If the rejection is based on facts within the personal knowledge of Patent Office personnel, an affidavit to support these facts is respectfully requested under 37 C.F.R. § 1.104(d)(2). Applicants respectfully assert that the initial burden which the law places on the Patent Office has not been met. Withdrawal of the rejection is respectfully requested.

Moreover, the written description requirement does not necessitate a demonstration of hypermutability in all bacterial species; rather, the written description requirement is satisfied by disclosure of a representative number of species of the genus. Applicants have demonstrated that hypermutability results from expression of the dominant negative mismatch repair proteins in two bacterial strains (BL21 and DH10B; Examples 2 and 3). As in *Amgen*, the demonstrated hypermutability in two bacterial strains adequately supports the claimed hypermutability in the claimed genus of bacterial cells.

Accordingly, the ordinarily skilled artisan would have recognized that Applicants were in possession of the invention for the full scope of the recited bacterial cells. Withdrawal of the rejection is respectfully requested.

The specification discloses a representative number of dominant negative mismatch repair proteins to adequately describe the recited genus of mismatch repair proteins.

The office action asserts that the specification is deficient in showing that truncation mutants other than human or *Arabidopsis thaliana* PMS2-134 mutants, PMSR proteins other than human PMSR3, or PMS2L protein would cause hypermutability in bacteria. (Office Action at pages 4-5.) The written description requirement does not necessitate a demonstration that expression of all of the mismatch repair proteins encompassed by the claims cause bacterial hypermutability. Rather, Applicants can fulfill the requirement by disclosing functional characteristics coupled with a known or disclosed correlation between function and structure. Guidelines for Examination, *supra.* This Applicants have done.

Applicants have demonstrated that dominant negative mismatch repair proteins from species as disparate as human and plant exert a dominant negative effect upon expression in bacteria to yield a hypermutable phenotype. (Specification at Examples 2 and 3.) Similarly, overexpression of wild-type mismatch repair alleles from species including human, mouse, plants, and yeast in bacteria has been shown to induce a dominant negative effect on the mismatch repair activity of the bacterial host. (Specification at page 11, lines 21-24; page 18, lines 1-8.) This evidences the strong conservation of the components of the mismatch repair pathway among a broad array of species. It further demonstrates a structure-function relationship between proteins with these structures and the function in the cells. One of skill in the art would thus recognize a correlation between structure (mismatch repair genes) and function (hypermutability)

Furthermore, Applicants have demonstrated three representative species of dominant negative mismatch repair proteins that exert a dominant negative effect when expressed in bacteria. Two truncation mutants of the PMS2 protein and the related PMSR3 protein produce a hypermutable phenotype when expressed in bacteria (Specification, Examples 2 and 3.) PMSR2, PMSR3, PMSR6, and PMS2L proteins were known to be highly

homologous to the N-terminal portion of PMS2 of the PMS2-134 mutant. Nicolaides *et al. Genomics*, 30:195-206 (1995). Thus applicants have taught that the art recognized structural similarity of the genus of recited mismatch repair proteins correlates with the dominant negative effect on mismatch repair in bacteria.

The office action has supplied no reason to doubt that mismatch repair proteins other than human PMS2-134, ATPMS134, or human PMSR3 would induce bacterial hypermutability. For example, the bare assertions that "[r]esults from human PMSR3 cannot be extrapolated to other genes in the PMSR family" (Office Action at page 5) or that shared homology between the dominant negative mismatch repair proteins is insufficient to establish structure-function correlation (Office Action at page 6) are wholly unsupported. An affidavit to support facts within the personal knowledge of Patent Office personnel is respectfully requested under 37 C.F.R. § 1.104(d)(2), if such facts are the basis for this ground of rejection.

Applicants respectfully assert that the Patent Office has not met its initial burden in making a rejection for alleged lack of adequate written description. It has presented neither evidence nor reasons why a person skilled in the art would not recognize that the specification provides a representative number of species of mismatch repair proteins recited in the claims. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a Notice of Allowance at an early date is respectfully requested.

Respectfully submitted,

Date: March 10, 2004

Sarah Kagan
Registration No. 32,141

Customer No. 22907